PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 55387.011 PCT	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/US04/19593	International filing date *(day/month/year)* 18 June 2004 (18.06.2004)	Priority date *(day/month/year)* 21 June 2003 (21.06.2003)
International Patent Classification (IPC) or national classification and IPC IPC: **H01J 49/40**(2006.01) USPC: 250/287,281,286,396R		
Applicant LECO CORPORATION		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 3 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *(sent to the applicant and to the International Bureau)* a total of 39 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) _____ , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:
   - ☒ Box No. I Basis of the report
   - ☐ Box No. II Priority
   - ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☐ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
26 January 2005 (26.01.2005)	08 May 2006 (08.05.2006)
Name and mailing address of the IPEA/ US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	Authorized officer Rhonda for Bell Nikita Wells Telephone No. (571) 272-2484

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US04/19593

Box No. I Basis of the report

1. With regard to the **language**, this report is based on:

☒ the international application in the language in which it was filed.

☐ a translation of the international application into English, which is the language of a translation furnished for the purposes of:

☐ international search (under Rules 12.3 and 23.1(b))

☐ publication of the international application (under Rule 12.4(a))

☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

☐ the international application as originally filed/furnished

☒ the description:
pages 45 as originally filed/furnished
pages* 1-33 received by this Authority on 26 January 2005 (26.01.2005)
pages* NONE received by this Authority on

☒ the claims:
pages NONE as originally filed/furnished
pages* 34-39 as amended (together with any statement) under Article 19
pages* 34-39 received by this Authority on 26 January 2005 (26.01.2005)
pages* NONE received by this Authority on

☒ the drawings:
pages 1/14 - 14/14 as originally filed/furnished
pages* NONE received by this Authority on
pages* NONE received by this Authority on

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. ☒ The amendments have resulted in the cancellation of:

☒ the description, pages 34-35
☐ the claims, Nos
☐ the drawings, sheets/figs
☐ the sequence listing (*specify*):
☐ any table(s) related to the sequence listing (*specify*):

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages
☐ the claims, Nos
☐ the drawings, sheets/figs
☐ the sequence listing (*specify*):
☐ any table(s) related to the sequence listing (*specify*):

** If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US04/19593

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 1-62	YES
	Claims NONE	NO
Inventive Step (IS)	Claims 1-62	YES
	Claims NONE	NO
Industrial Applicability (IA)	Claims 1-62	YES
	Claims NONE	NO

2. Citations and Explanations (Rule 70.7)

Claims 1-62 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest a multiple-reflecting time-of-flight mass spectrometer (MR-TOF-MS) composed of at least one reflection by the ion mirror assembly for separating ions in time according to their mass-to-charge ratio so that a flight time of the ions is independent of the ion energy (ref to the independent claim 1).

With respect to the independent claims 33, 48, and 61, prior art does not teach or fairly suggest a multiple-reflecting time-of-flight mass spectrometer which comprises at least two grid-less ion mirrors separated by a drift space and substantially elongated in one shift direction. The dependent claims are allowable due to their dependence upon their rspective independent claims.

---------- NEW CITATIONS ----------

US 6,674,069 B1 (Martin et al.) 06 January 2004, see column 3, lines 14-31.

PCT/US04/19593 .26012005

MULTI-REFLECTING TIME-OF-FLIGHT MASS SPECTROMETER AND METHOD OF USE

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

The invention relates generally to the field of mass spectrometry, and particularly to the field of analysis using multi-reflecting time-of-flight mass spectrometers (MR-TOF MS) and methods for using those instruments.

STATE OF THE ART

Mass spectrometry is a well recognized tool of analytical chemistry. The instruments assist in the identification and quantitative analysis of various compounds and mixtures. The sensitivity and resolution of mass spectrometric instruments is an important concern for practical use. It has been recognized that the resolution of time-of-flight mass spectrometers (TOF MS) is proportional to the length of the flight path. However it has been difficult to increase the flight path while keeping the size of the instrument to a reasonable size. One proposed solution for increasing the flight path involved bouncing the ion beam to produce a reflection within the time-of-flight mass spectrometer (MR-TOF-MS). The use of an actual MR-TOF MS became possible after the introduction of an electrostatic ion mirror incorporating time-of-flight focusing properties. United States patent 4,072,862 referenced Soviet patent SU198034, and to an article appearing in the journal Sov. J.Tech.Phys. 41, (1971) 1498, where an ion mirror was disclosed for improving the time-of-flight focusing with respect to the ion energy spread in a time-of-flight spectrometer. The use of an ion mirror effectively tripled the length of the flight path by creating a single folding ion flight path.

H. Wollnik realized the potential of ion mirrors in MR-TOF MS. United Kingdom patent GB2080021 suggests a way of reducing the full length of the instrument by folding the ion path between multiple mirrors. Two rows of such mirrors were either aligned in the same plane or located on two opposite parallel circles (Fig.1). Introduction of the ion mirrors with the spatial ion-focusing reduced ion losses and kept the ion beam confined regardless of the number of reflections. Additional details are reported in U.S. patent 5017780. The ion mirrors disclosed in the U.K. '021 patent, mentioned above, also provided ion flight times independent of the ion energy.

Two types of MR-TOF MS are disclosed in this application, including: (a) a 'folded path' configuration, that is generally equivalent to combining N-sequential reflecting TOF MS, where the flight path is folded along a jig-saw trajectory; and (b) a 'coaxial reflecting'

configuration which employs multiple ion-reflections between two axially-aligned ion mirrors using pulsed ion admission and release. The 'coaxial reflecting' configuration is also described by H. Wollnik et.al. in Mass Spec. Rev., 1993, 12, p. 109, and is implemented in the work published in the Int. J. Mass Spect. Ion Proc. 227 (2003) 217. Resolution of 50,000 is achieved after 50 reflections (turns) in a moderate size (30cm) TOF MS. Grid-less and spatial-focusing ion mirrors indeed preserve ions of interest (losses are below factor of 2), although the admitted mass-range shrinks proportionally with the number of cycles.

A cyclic MR-TOF MS is described by H. Wollnik, in Nucl. Instr. Meth., A258 (1987) 289, and by Sakurai et al, Nucl. Instr. Meth., A427 (1999) 182. There ions were kept in closed orbits using electrostatic or magnetic deflectors. Usually this scheme would employ multiple repetitive cycles, which would shrink mass range similar to the coaxial reflecting scheme.

A more sophisticated folded-path MR-TOF MS was disclosed in Soviet Union publication SU1725289 by Nazarenko et al. (1989). There the system used two-dimensional grid-less mirrors. The Nazarenko MR-TOF MS provided two identical mirrors, built of bars, parallel and symmetric with respect to the median plane passing between the mirrors and also to the plane of the folded ion-path (Fig. 2). The mirror geometry and potentials were arranged to focus the ion beam spatially across the plane of the folded ion-path and to provide second-order time-of-flight focusing with respect to the ion energy. The ions experienced multiple reflections between the planar mirrors while the slowly drifted toward the detector ("shift direction" and in that instance the X axis). The number of cycles and resolution could be adjusted by varying the ion injection angle.

The work of Nazarenko et al. shares one aspect with the present invention; that of providing a folded ion-path MR-TOF MS with planar ion mirrors having spatial and time-of-flight focus properties. However the Nazarenko et al. device does not provide ion focusing in the shift direction, essentially limiting the number of reflection cycles. Like the prior art, Nazarenko's ion mirrors also did not provide time-of-flight focusing with respect to the spatial ion-spread across the plane of the folded ion-path, so that use of a diverging or a wide ion beam would have ruined the time-of-flight resolution and would make an extension of the flight path pointless. In other words, the scheme would fail to deliver an acceptable analyzer, and thus an ability of working with real ion-sources. Lastly Nazarenko's device was unable to receive different types of ion sources, nor an efficient means for coupling the MR-TOF MS with various ion sources.

The type of ion source, the spatial and timing characteristics of the ion beam, and the geometrical constraints of the analyzer are important considerations in the design of a MR-TOF MS. Compatibility with a single-reflecting TOF MS does not automatically mean that a source

is well suited for a MR-TOF MS. For example, pulsed ion sources, like SIMS or matrix-assisted desorption/ionization MALDI, are compatible with TOF MS and such instruments are characterized by high resolution and moderate ion losses caused by spatial ion divergence. Switching to MR-TOF MS introduces new problems. On one hand, the pulsed nature of such sources compliments an extension of the flight time in MR-TOF MS since the frequency of ionizing pulses is adjustable. On the other hand, instability of MALDI ions is a limiting factor on flight time extension. A use of MR-TOF MS would also reduce solid angle of the detector proportionally to the square of the total ion flight-path, thus deteriorating sensitivity.

Gaseous ion sources, like electrospray ionizers (ESI), atmospheric pressure chemical ionization, (APCI) atmospheric pressure photo-ionization (APPI), electron impact (EI), chemical ionization (CI), photo-ionization (CI) or inductively-coupled plasma (ICP) are known to produce stable ions, but they generate an intrinsically continuous ion beam or quasi-continuous ion beam similar to the recently introduced gas-filled MALDI ion source described in United States patents 6,331,702 and 6,504,150. Time-of-flight MS has been successfully coupled with continuous (and later to quasi-continuous) ion sources after the introduction of an orthogonal ion acceleration configuration ("O-TOF MS"), (See also WO9103071 and Soviet patent SU1681340), efficiently converting continuous ion beams into ion pulsed-packets. Gaseous ion sources in combination with a collisional-cooling ion guide (US4963736) produced cold ion beams with low-velocity spread along the axis of TOF MS, which helped to achieve high TOF resolution in excess of 10,000. However, using MR-TOF MS would reduce the duty cycle of the orthogonal acceleration and thus drop sensitivity.

United States patent 6,107,625 suggested that a further increase of the resolution of O-TOF MS would be limited by a so-called 'turn-around time' and increasing of the flight path to improve resolution. The '625 patent specification suggested coupling an external electro-spray ionization (ESI) source to a 'coaxial reflecting' MR-TOF MS via an orthogonal accelerator, combined with an ion mirror and multiple deflectors such as shown in Fig.3. To improve the sampling of the continuous ion-beam the interface employed a linear ion trap, storing ions between rare ion pulses. In the article by Melvin Park et al. entitled, "Analytical Figure of Merits of a Multi-Pass Time-of-Flight Mass Spectrometer"(extended abstract on ASMS 2001, www.asms.org), the MR-TOF MS had a demonstrated resolution of 60,000 using 6 cycles of reflections in a c.a. 1m long instrument. However, the use of ion mirrors with grids caused severe ion scattering and ion loss. Coaxial reflecting MR-TOF MS improved the resolution but reduced the mass range proportionally.

Electro-spray ionization with orthogonal injection has also been coupled to an MR-TOF MS with a folded ion-path (see European Patent 1237044 A2 and the article written by J. Hoyes

et al. in extended abstract ASMS 2000 entitled, 'A High Resolution Orthogonal TOF with Selectable Drift Length (www.asms.org)). The device allowed for the conversion of existing commercial O-TOF MS into dual-reflecting instruments by introducing an additional short reflector between the orthogonal source and the detector. The number of ion reflections was controlled by adjusting the energy of the continuous ion-beam. The 'folded path' MR-TOF MS retained full mass-range and considerably improved resolution, but it also severely reduced the duty cycle and the geometrical efficiency of ion sampling into the orthogonal accelerator. The two examples described above demonstrate that a conventional orthogonal acceleration becomes inefficient in MR-TOF MS, particularly at extended flight-times.

There have been multiple attempts at improving pulsed-ion sampling from continuous ion-beams, mostly employing ion storing in radio-frequency (RF) traps similar to the 3-D ion traps (IT) and the linear ion traps (LIT) described in U.S. patents 5,763,878 and 6,545,268 and in PCT publication WO9930350 and dual LIT described in GB2378312. Since all of those solutions compromised temporal and/or spatial distribution of the ejected ion-packets, the orthogonal injection was still the method of choice for singly-reflecting TOF MS. Some trapping features were used in an intermediate scheme described in U.S. patent 6020586 that combined both ion trapping and orthogonal acceleration. Slow ion-packets were periodically ejected from the storing ion-guide into the synchronized orthogonal accelerator. Compared to conventional O-TOF MS, the scheme improved sensitivity, while it moderately sacrificed resolution and mass range.

Summarizing the above, the previous MR-TOF MS did not offer a combined spatial and time of-flight focusing to maintain the ion beam along a substantially extended flight path. Most of the previous references described MR-TOF analyzers without consideration of the compatibility with the ion sources. In fact, the limited acceptance of the known MR-TOF analyzers seriously limited such coupling and was expected to cause significant ion loss over substantially elongated flight paths. Some references have been made to actual coupling of MR-TOF MS to continuous ion sources, demonstrating strong improvement of resolution. However, resolution was gained at the expense of sensitivity and, in the case of coaxial reflections, at the expense of a sever reduction in the mass-range. Therefore, there is an existing need for a time-of-flight mass spectrometer working with intrinsically continuous and/or quasi-continuous ion sources and superior to O-TOF MS in terms of analytical characteristics, namely – sensitivity, mass range and resolution.

SUMMARY OF THE INVENTION

The inventors have discovered that the acceptance and resolution of MR-TOF MS using two-dimensional planar mirrors could be substantially improved by placing a periodic lens assembly and a predetermined geometry of planar mirrors in the drift space for providing focusing in the drift direction as well as time-of-flight focusing with respect to the spatial spread of the ions.

The inventors further discovered that an improved acceptance of the MR-TOF MS of the invention provides efficient coupling to continuous ion sources via an ion storing device. Continuously-arriving ions could be stored and pulse ejected from the storing device, such as an ion guide, IT, or LIT, thus saving ions between rare pulses of the MR-TOF MS, sparse compared to O-TOF MS.

The MR-TOF MS of the invention provides an advantageous combination of ion optic features when compared to the prior art devices. The invention offers a full mass range, a 'folded path' configuration, eliminates ion loss associated with mesh since the ion mirrors are without a grid; efficiently consumes continuous ion beams by storing the ions in an ion trap with pulsed-ion ejection at lower frequencies; and accepts a wide ion-beam from the ion traps since the analyzer has a spatial focusing by a periodic lens in the shift direction. Spatial focusing is also provided by mirrors located across the plane of the folded ion-path. The invention improves resolution by providing a high-order time-of-flight focusing with respect to ion energy and to the spatially spread ion packets. The invention tolerates a larger turn-around time of the ion packets by extending the flight time using a folded ion path produced by multiple reflections of a well-confined ion beam. Lastly the longer flight time of the invention includes a by-product advantage – a slower and less expensive detector and data acquisition system, both currently costly parts.

The invention introduces a completely novel feature and function to MR-TOF MS - multiple lenses, optimally positioned in the middle of the flight-tube drift space with a period corresponding to the ion shift per integer number of turns. The periodic lens assembly allows focusing of the ion beam and thus insures a stable confinement of the ions along the extended folded ion-flight path. The lens assembly brings a novel quality to MR TOF: the beam spatial and angular spreads stay-limited even after an extremely large number of reflections (actually achieved if using reflections in the shift direction). Even more, using ion-optics simulation the inventors discovered that ion motion in the novel MR-TOF efficiently withstands various external distortions like inaccuracy of geometry, stray electric and magnetic fields of pumps and gauges, as well as a space charge of the ion beam itself. The MR-TOF returns ions in the vicinity of the main trajectory in spite of those distortions, similar to trapping in the potential

groove. The use of the periodic lens assembly allows compact packaging of MR-TOF MS with the extended flight path, combined with a confident full transmission of the ion beam.

Tuning of the lens assembly allows periodic, repeatable focusing in the shift direction achieved when the focal length (F) matches an integer number of the half reflections or a quarter of the full ion turns (P/4), F=N*P/4. The tightest focusing may occur when F=P/4. Such tight focusing is advantageous for minimizing the shift-per-turn and making the instrument more compact. Even under the condition of tight focusing, lenses remain weak because of a relatively long ion-path per turn, and therefore they introduce only minor incorrigible time-of-flight aberrations with respect to the ion spatial spread in the plane of the folded ion-path. Planar lenses, substantially elongated across the plane of the ion path, provide an advantage of fairly independent tuning of the spatial focusing by ion mirrors and periodic lenses, since they focus in different directions. Besides, such lens assemblies may also incorporate steering by using asymmetric voltages on side plates.

The invention further permits an increase in the length of the flight path by employing reflections in the shift direction. Such reflections can be achieved, for example, by steering in (asymmetrically operated) lenses. The deflection plates may operate substantially continuously or in a pulsed mode to permit ion gating. A single reflection would not affect the mass range, but a further increase in the length of the flight path by additional reflections would impact mass range. The deflection plates could be also used to bypass the analyzer and to steer the ions into the receiver.

Novel focusing properties of the mirrors used in the invention are provided by choosing a proper distance between the mirrors and an adjustment of the electrode potentials. Such adjustments result in 3rd-order time-of-flight focusing of the ion energy, 2nd-order time-of-flight focusing with respect to the spatial ion spread across the plane of the folded ion-path, and spatial focusing across the plane. The inventors discovered that the elimination of high-order time-of-flight aberrations is stable with respect to assembly defects as well as to moderate variations of the drift lengths and electrode potentials. Therefore, a high resolving-power may be obtained by tuning the novel MR-TOF MS while adjusting at least one electrode potential, in fact, varying one parameter – a linear dependence of the ion flight-time on the ion energy.

The focusing properties described above are realized, for example, in the planar arrangement of 4-electrode mirrors, composed of square frames, substantially elongated in a shift direction. The desired field structure could also be made using slotted plates, bars, cylinders, or curved electrodes. The edges of the two-dimensional mirrors could be efficiently terminated using printed circuit boards to shorten the total physical length of the MR-TOF MS. Having more electrodes is likely to improve mirror parameters.

In a preferred mode of operation, the ion source and the ion detector are located in the flight tube drift-space between the mirrors. In such a configuration the folded ion-path remains far from the mirror edges and the mirrors can be operated in a constant mode to achieve better stability and mass accuracy for the MR-TOF MS. The invention is compatible with pulsed ion-admission from an external source or ion release through ion mirrors in order to couple the MR-TOF MS with external ion sources or ion receivers and to avoid beam passage through fringing fields of the mirror edges.

The invention is applicable to various ion sources, including pulsed ion sources such as MALDI or SIMS, quasi-continuous ion sources such as MALDI with collisional cooling, as well as intrinsically continuous ion sources like ESI, EI, CI, PI, ICP or a fragmenting cell of a tandem mass spectrometer. All continuous or quasi-continuous ion sources preferably operate with an ion guide.

As briefly touch on above, the invention may also be used in conjunction with an ion storing device lessening, if not avoiding, ion losses between rare accelerating pulses. Such ion storing may occur in gas-filled radio-frequency (RF) storing devices of various kinds, including, but not limited to, ion guides, RF channels, IT or LIT, incorporated either into an ion source itself or into an accelerator of the MR-TOF MS. The invention may employ either a direct acceleration out from an ion storing device, axial or orthogonal, or a dual acceleration scheme where a slow ion-pulse is ejected out from the storing device with consecutively-pulsed acceleration, axial or orthogonal, or a dual storage scheme where slow ion-pulses are admitted into the second ion trap operated at a lower gas pressure. Ion ejection from the second storing device may also be achieved axially or orthogonally, or via an additional accelerator, axial or orthogonal. Some compromises in parameters of ion packets are acceptable because of the substantial extension of the flight path and the wide acceptance of the novel MR-TOF MS.

One embodiment of the invention employs the latter, more complex but advantageous scheme of dual ion storage. Ion guides are a preferred choice for both storage devices. It is also preferable to use an additional set of pulsed electrodes whose field penetrates well into the ion storage area of the second ion guide and permits fast ion ejection in the axial direction with a small turn-around-time while providing a fairly uniform accelerating field and a moderate ion divergence. Compared to orthogonal acceleration schemes the invention provides an almost complete utilization of the continuous ion-beam. Some increase of the turn-around-time is compensated by an extension of the flight path. This scheme is expected to provide a complete utilization of the continuous or quasi-continuous ion beam as well as an improved resolution in the range of R~100,000. The MR-TOF MS could be used either as a stand-alone instrument or as a part of LC-MS or MS-MS tandem device, and mostly expected as a second analyzer of

fragment ions combined with any known mass separator of parent ions and any known kind of fragmenting cell.

The invention further highlights several novel ion storing devices such as hybrid ion traps composed of one or more ion guide and 3-D ion traps with open ring electrodes. Simulations of the segmented analog have shown feasibility of such traps for the preparation of ions in MR-TOF analysis. Another novel device may comprise a linear ion trap with auxiliary electrodes. Both ion trapping and axial ejection could be achieved by pulsing voltages on separate sets of electrodes without affecting any RF voltages.

The invention is expected to provide more intense ion pulses, hence the dynamic range and useful life of the ion detector become an important issue. Multiple solutions are known in the art including ion suppression either at the ion storage devices, or at the mass separation or detection stages. The known strategies include automatic adjustment of ion intensity or mass filtering of unwanted beam components. Dynamic range is enhanced by using a secondary electron multiplier (SEM) and analog-to-digital converters (ADC) in data acquisition. A specific and significant feature of the invention is a longer pulse duration, allowing lower bandwidth and somewhat easier solutions of the above problems.

The MR-TOF MS of the invention may be used as a first separating mass spectrometer in a tandem mass-spectrometer arrangement. The advantage of using an MR-TOF is more specifically set forth in a co-pending patent application filed by one of the inventors. The co-pending invention describes using a slower TOF1 for ion separation combined with a fast TOF2 for fragment analysis. The arrangement permits parallel analysis of multiple precursors per single pulse from the ion source. The present invention provides particularly long separation in MR-TOF MS, as well as separation at low and medium ion beam energy, tight focusing of the ion beam, precise control of the ion beam location and useful while directing the beam into a fragmenting cell.

These and other advantages of the invention will become apparent to one of ordinary skill in the art after reading the following detailed description of the invention with reference to the appended drawing figures, described in greater detail below.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 illustrates a multi-reflecting time-of-flight mass spectrometer (MR-TOF MS) disclosed in GB Patent No. 2080021;

Fig. 2 generally illustrates a prototype design of a 'folded path' MR-TOF MS;

Fig. 3 illustrates one design for a 'coaxially reflecting' MR-TOF MS;

Fig. 4 schematically illustrate one embodiment of an MR-TOF MS of the invention using periodic lenses;

Fig. 5 illustrate an embodiment of the geometry and potentials of ion mirrors providing a new and unobvious spatial and time-of-flight focusing for the invention;

Fig. 6 schematically illustrate principles of ion-path extension by ion reflection in the shift direction utilized in one embodiment of the invention;

Fig. 7 is generalized schematic diagram of ion sampling from a continuous ion source into the invention using an intermediate ion storage device;

Fig. 7A represents a block diagram of a pulsed ion-source in the invention;

Fig. 7B illustrates the use of an electrospray ion source as an example of the continuous ion;

Fig. 7C illustrates a MALDI ion source with collisional dampening as an example of the quasi-continuous ion source;

Fig. 7D schematically details one embodiment of an intermediate storage ion guide;

Fig. 8 shows a schematic of a second ion storage device and of the ion accelerator;

Fig. 9 is a block diagram of a dual ion storage device with axial ejection and with an optional accelerator;

Fig.10 illustrates one arrangement of a second storage device providing pulsed axial ion ejection;

Fig. 11 illustrates one arrangement of orthogonal acceleration from a non-storing ion guide;

Fig. 12 illustrates one arrangement of a second storage device forming a hybrid of a quadrupole ion guide and a 3-D quadrupole ion trap;

Fig. 13 illustrates a segmented analog of the hybrid trap;

Fig. 14 shows schematics of a preferred embodiment of the MR-TOF MS comprising the invention;

Fig. 15 schematically illustrates a preferred embodiment of a tandem mass spectrometer with parallel MS-MS analysis and a MR-TOF MS as a first MS stage of slow separation of parent ions;

Fig. 16 schematically shows the preferred embodiment of a tandem mass spectrometer with two MS stages providing a versatile switching between high throughput and high-resolution modes of MS-MS analysis; and

Fig. 17 illustrates an embodiment of a mass spectrometer for multistage MS^n analysis employing at least one MR-TOF MS analyzer and a fragmentation cell, reverting ion flow.

DESCRIPTION OF THE VARIOUS EMBODIMENTS

The present invention relates generally to the area of mass-spectroscopic analysis, and more particularly to multi-reflecting time-of-flight mass spectrometry (MR TOF MS). More specifically, the invention relates to the improved resolution and sensitivity obtained in planar and gridless MR-TOF MS by employing a novel arrangement and control of mirror electrodes in combination with a periodic set of lenses in the ion drift space. Because of improved spatial and time focusing the invention will have a wider acceptance and confident confinement of an ion beam along an extended folded ion-path. As a result, the MR-TOF MS comprising the invention may be efficiently coupled to continuous ion-sources via an ion storage device thus substantially improving the duty cycle for ion sampling. The invention may also be used in tandem mass spectrometers, as a first slow-separator in a tandem two-dimensional parallel MS-MS analysis; as a second high-resolution mass analyzer combined with any known type of separator; or in tandem employing MR-TOF MS at both stages of analysis.

Fig.1 illustrates a multi-reflecting time-of-flight mass spectrometer (MR-TOF MS) described by Wollnik et.al. in GB Patent No. 2080021 (fig.3 and fig.4 of the GB patent). In such a time-of-flight mass spectrometer ions of different masses and energies are emitted by a source 12. The flight path of the ions to a collector 20 is folded by arranging for multiple reflections of the ions by mirrors R1, R2, ... Rn. The mirrors are such that the ion flight time is independent of ion energy. Wollnik et al. shows two geometrical arrangements of multiple axially-symmetric ion mirrors. In both arrangements ion mirrors are located in two parallel planes I and II and are aligned along the surface of the ion path. In one arrangement this surface is a plane and in another the surface is in the form of a cylinder. Note that the ions travel at an angle to the optical axis of the ion mirrors which induces additional time-of-flight aberrations and thus considerably complicates achieving high resolution.

Fig. 2 shows a 'folded path' MR-TOF MS of a prototype by Nazarenko et.al., described in Russian Patent SU1725289. The Nazarenko MR-TOF MS comprises two grid-less electrostatic mirrors each composed of three electrodes 3, 4 and 5 in one mirror, and 6, 7 and 8 for another mirror. Each electrode is made of a pair of parallel plates ('a' and 'b'), arranged symmetrically with respect to the 'central' plane XZ. A source 1 and receiver 2 are located in the flight tube drift-space between the ion mirrors. The mirrors provide multiple ion reflections with the number of reflections being adjusted by moving the ion source along the X axis relative to the detector. Nazarenko describes a type of ion focusing occurring on each ion turn to achieve spatial ion focusing in the Y direction and a second order time-of-flight focusing with respect to the ion energy. It is significant to note that Nazarenko provides no ion focusing in the shift direction, thus essentially limiting the number of reflection cycles. It is also important

to note that Nazarenko does not provide time-of-flight focusing with respect to spatial ion spread in the Y direction. As a result Nazarenko fails to deliver a wide acceptance of analyzer and thus an ability of working with real ion sources. Lastly, the Nazarenko device makes no suggestion of the type of ion source, nor of efficient ways of coupling an MR-TOF MS to various ion sources.

Fig. 3 shows a 'coaxial-reflecting' MR-TOF MS disclosed in US Patent No. 6,107,625. The '625 system comprises two electrostatic reflectors 34 and 38 positioned coaxially with respect to one another such that ions generated by an ion source 32 can be reflected back and forth between the reflectors. The first reflecting device 34 combines the functions of an orthogonal accelerator and an ion mirror. After multiple ion reflections each of the mirrors is rapidly switched off to allow the ions to pass through the reflector and onto the ion detector 36. The '625 patent teaches a manner of coupling a continuous ion source to an MR-TOF MS. The described apparatus indeed achieves high resolution within a small size instrument. However, an employed 'coaxial reflecting' scheme strongly reduces mass range and decreases the duty cycle of ion sampling from a continuous ion beam. Meshes cause substantial ion losses. The duty cycle is improved in a later work by the author after introducing a generic ion storage device into the interface.

Fig. 4 is a schematic of one embodiment of the invention comprising a MR-TOF MS having a novel periodic lens. The MR-TOF MS 11 comprises a pulsed ion source 12 with a built-in accelerator 13, an ion receiver 16, and at least one set of two grid-less ion mirrors 15 oriented parallel to each other and substantially elongated in a 'shift' direction denoted here as the Y-axis. A field-free space 14 is defined between the mirrors 15 and includes at least one set of lenses 17 positioned in the drift space. These elements are arranged to provide a folded ion path 19 between the ion source 12 and the ion receiver 16. The ion path 19 is defined by the path of the multiple reflections of the ions between the mirrors 15 and the ion drift in the shift-Y direction. The shift is arranged by a slight tilting, mechanically or electronically, of the incoming ion packets with respect to the X axis. The lenses 17 may be positioned along the Y-axis with a period corresponding to the ion shift per integer number of ion reflections. The preferred embodiment strongly enhances acceptance of the MR-TOF MS by providing novel ion optic properties - periodic focusing by lenses 17 in the shift Y direction, and complementing periodic spatial focusing in the orthogonal Z direction provided by planar grid-less ion mirrors. The ion optic properties as well as the improved time-of-flight focusing by the specially-designed ion mirrors are discussed in greater detail below.

Incorporation of the periodic lenses 17 is a completely novel feature in MR-TOF MS of the invention by providing stable retention of the ions along the interlaced ion path. Lens tuning

allows periodic, repeatable focusing in a shift direction achieved when the focal length F matches an integer number of the half reflections or quarters of full ion turns (P/4), F=N*P/4. It is believed the best focusing occurs when F=P/4. Such tight focusing is advantageous in minimizing the amount of shift per turn and making the instrument more compact. Even with tight focusing the lenses 17 remain weak because of a relatively long ion path-per-turn and introduces only minor incorrigible time-of-flight aberrations with respect to the ion spatial-spread in the plane of the folded ion-path. Planar lenses, substantially elongated across the ion path provide an advantage of fairly independent tuning of spatial focusing by ion mirrors and lenses both across and in the plane of the folded ion path, respectively. Besides, such lenses may also incorporate steering by using asymmetric voltages on side plates.

The set of periodic lenses within the MR TOF are intended to limit beam parameters even after an extremely large number of reflections (actually achieved if using reflections in the shift direction). Through ion optics simulation the inventors discovered that ion motion in the invention efficiently withstands external distortions, like inaccuracies of geometry, stray electric and magnetic fields of surfaces, pumps and gauges, as well as space charge of the ion beam. The MR-TOF returns ions into the vicinity of main trajectory in spite of those distortions, equivalent to trapping in the potential groove. The periodic lenses 17 allow compact packaging of the MR-TOF MS with an extended flight path combined with confident full transmission of the ion beam.

Fig. 4 also illustrates a side view 21 of the same embodiment as well as an axial potential distribution 22 in the analyzer of the invention. The mirrors 15 are shown symmetric with respect to the XY plane and preferably, though not necessarily, identical with respect to each other, i.e. are symmetric around the YZ plane. The mirrors 15 may be composed of at least one or more electrodes (an example is four) to define a lens electrode 15L, two electrodes 15E and a cap electrode 15C in addition to a specially formed edge of the drift space 14D. As mentioned, the mirrors are preferably elongated in a shift direction to form a two-dimensional electrostatic field around the area of the folded ion-path 19.

Novel focusing properties of the mirrors are obtained by selecting a preferred distance between the mirrors and an adjustment of the electrode potentials. The inventors have found such parameters by ion optic simulations with a built-in calculation of derivatives and also with a built-in automatic optimization block. Working with a computer program the inventors have formulated some general trends of an optimization algorithm and several key requirements to the ion optics of the ion mirrors. For example, in the case of a symmetric MR-TOF MS having two identical mirrors, each mirror should comprise a plurality of electrodes such as at least 4, in order to have 5 independently tuned parameters: 3 parameters (optimally two electrode

potentials and the drift length between the mirrors) are chosen to provide a periodic (after each reflection) third-order time-of-flight focusing with respect to energy, i.e. the tuning allows elimination of the first, second and third-order derivatives of the ion flight-time on the ion energy; one parameter (optimally the potential of the 'incorporated lens' electrode closest to the drift space) provides a so-called 'parallel-to-point' spatial focusing across the plane of the folded ion path. "Parallel-to-point" is preferably interpreted to mean that a parallel ion packet starting in the middle of drift space will be focused into a point after one-half of a turn and will be converted back into a parallel ion packet after one full turn. Advantageously this focusing is arranged so that the ions of the packet also intersect a plane of the ion path in the vicinity of the turning point. One remaining parameter is adjusted to eliminate the second-order derivative of the flight time of the just-mentioned ion packet with respect to the initial ion offset from the plane of the folded ion path. If both conditions are satisfied, then the symmetry of the mirror arrangement automatically leads to an elimination of all time-of-flight aberrations up to the second order on the initial coordinate and the angular spread across the plane of the folded ion path after each full turn after an even number of reflections. The inventors realized that elimination of high-order time-of-flight aberrations would be stable with respect to assembly defects as well as to moderate variations of the drift lengths and electrode potentials. Therefore, a high resolving-power could be obtained by tuning of the MR-TOF MS while adjusting one electrode potential: in fact, varying one parameter – a linear dependence of the ion flight time on the ion energy.

Fig. 5 illustrates examples of geometry and voltages for an MR-TOF analyzer comprising the invention which provides the aforementioned high-order spatial and time-of-flight focusing. The view 23 shows dimensions of the exemplary four- electrode mirror briefly mentioned above, with sizes being normalized to a length L of a typical electrode. As before, the electrodes of the mirror are denoted as 15L for the lens electrode, 15E for the two middle electrodes and 15C for the cap electrode. Similarly, the view 24 shows dimensions of the drift space and of the entire mirror. View 25 shows potentials on the electrodes of the same particular MR-TOF MS. The potentials are normalized to the nominal energy E of the ion beam. The analyzer forms an axial potential distribution similar to the one shown in view 22 of Fig. 4.

The elongated two-dimensional structure of the ion mirror could be formed using electrodes of various shapes. Fig. 5 shows a few possible types of electrode geometry, including elongated square frames, slotted elongated plates, and square bars. Not shown are the types formed by parallel rods, and curved electrodes like cones, hyperbolas, etc. The inventors also expect that a desired electric field structure could be synthesized using a fewer number of

two-dimensionally shaped electrodes. To preserve a two-dimensional field structure requires a special treatment of a boundary problem. To avoid distortions of the field structure the mirrors are either made much longer than the total shift of the folded ion path, or employ special devices. One example could include fine-structured printed circuit boards (PCB) 30 with a shape of electrodes repeating a shape of equipotential lines of the mirror field. In the inventor's ion optics simulations it was found that a simple adjustment of the width of the lens edge allowed a noticeable reduction of the fringing field penetration. Similar results could be obtained by introducing an additional edge electrode. One example may be a rib of the lens electrode 15L.

Fig. 6 schematically illustrates the principles of ion path extension by ion reflections in the shift direction within one embodiment of the MR-TOF analyzer forming the invention. In addition to standard components (shown using the same reference numbers), the embodiment 31 comprises a plurality of steering devices 32 and 33 and an optional in-line ion receiver 34. The incident ion-packet 33 can be either deflected onto an additional detector 34 or steered into the MR-TOF MS along the folded path 36. On the other end of the shift-axis Y the second steering device 35 can either release ions onto the ion receiver 16 or steer the ion packet again into the MR-TOF MS along the folded ion path 37.

In operation, in a particular regime, when the entrance steering 32 is disabled and the exit steering 33 is constantly on, the MR-TOF MS retains a non-repeating folded ion path and thus retains a full mass range of mass spectrometric analysis while doubling the flight path. The entrance steering can be used to by-pass the analyzer entirely. This feature is described in much greater detail in a co-pending patent application where a MR-TOF MS is used as an ion separator in a tandem MS and the bypass feature allows toggling between the tandem and the MS-only regimes. The steering could be used to pass the ion packets along a repetitive, cyclic folded ion-path where an increase of the flight path length appears to be accompanied by a proportional reduction of the mass range; a compromise to be made upon requirements of a particular application. Geometrical constraints of the entire analyzer and the fringing field of the mirror edges may become important while using reflections in the drift direction. An optional way around the problem is by passing the ion beam through ion mirrors, more specifically through a slit formed in the mirror cap electrode 15C. The mirror 15 then can be extended, e.g. as shown by dashed line, and should be turned on and off in a pulsed mode.

One example 41 of a steering device is illustrated in Fig. 6. The steering device 41 comprises at least one, and preferably a set of parallel plates 42 to 46 where the plates 42 are grounded. The steering device 41 combines the features of planar deflecting plates and a planar lens. The steering device 41 may be either toggled between two functions or combined to

provide two functions simultaneously by tuning voltages on plates 44 and 45. The device 41 allows incorporation into a periodic structure of lenses. In this case, each individual cell could be used for both ion focusing and/or reflection in the drift direction. The deflection plates could operate constantly or in a pulsed mode to allow ion gating, selecting narrow mass range, analyzing multiple precursors or multiple mass windows simultaneously. Flexible switching between the lenses and the deflectors may also be useful in overcoming the problem of fringing fields since the deflectors can create a closed loop well within the boundaries of the unaffected mirror field (not shown).

The introduction of ion deflection causes compromises in the time-of-flight resolution; hence they are generally used for ion manipulation and the extension of flight time rather than for improving resolution of the MR-TOF MS. For example, with a typical energy spread of five percent (5 %) and a phase space of the beam of approximately 10π mm mrad in both directions normal to the beam path, an ion optical simulation of the MR TOF MS of the invention with L = 25 mm predicts an achievable mass resolving power (FWHM) of 100,000 without using deflectors in the mode with the maximal focal length of the lenses is equal to the length of the full beam turn (two reflections). With the tightest focusing induced by the lenses and the additional use of the deflectors, the resolving power drops to approximately 30,000. Note however that because of the extended flight time, this value can be achieved even for significantly larger ion turn-around-times as compared to the conventional TOF MS having the same resolving power.

Now that we have completed a description of the different embodiments of the MR-TOF MS it is of particular importance to note that the novel MR-TOF analyzer has a much higher tolerance to spatial and temporal spreading of the ion beam. The novel analyzer provides a stable ion beam confinement that allows an extension of the flight time without causing substantial geometrical ion losses. An extended flight time, in turn, enhances TOF resolution and reduces the effect of ion turn-around-time appearing in the pulsed ion source. Finally, the MR-TOF MS of the invention also provides high order time-of-flight focusing with respect to the spatial spread of the initial ion beam, i.e. much wider beams can be accepted without loosing time-of-flight resolution. On the other hand, an extension of the flight time reduces the efficiency of ion sampling from continuous ion beams. The contradiction is resolved by another feature of the invention – the incorporation of ion storing and pulse ejection into a continuous or quasi-continuous ion source.

The invention strongly improves efficiency of ion sampling into an MR-TOF MS by adding an ion storing step for the accumulation of the continuous ion beam and pulsed-ion ejection at a reduced frequency, corresponding to an extended flight time of the MR-TOF MS.

The ion storing occurs in gas-filled, radio-frequency (RF) storing devices of various kinds, including ion guides, RF channels, and IT or LIT, incorporated either into an ion source itself or into an accelerator of the MR-TOF MS. The storing step avoids ion losses occurring between rare pulses of any MR-TOF MS. This combination has not been described in the prior art.

Fig.7 is a generalized schematic showing ion sampling from continuous ion sources into the MR-TOF MS of the invention using an intermediate ion storage device, wherein Fig 7A shows a block diagram of the entire MR-TOF MS; Fig. 7B shows details of the ion source and of the ion guide; and Fig. 7C shows details of the second storage device and of the ion accelerator. With reference to Fig 7A, and using a block diagram level of detailing, the entire MR-TOF MS of the preferred embodiment of the invention 51 comprises a continuous ion source 61, an ion guide 71, a second storage device 81, an accelerator 91, and an MR-TOF analyzer 31, being sequentially interconnected. The block diagram shows the most general case. One or more of elements 71, 81 and 91 may be optional. That is to say in different embodiments, one or more of the elements 71, 81 and 91 may be integrated into other components or assemblies or partially omitted from the device.

The major function of an additional storing device 81 is to prepare an ion cloud at different conditions compared to the rest of ions stored in the first storing ion guide 71. Such conditions may differ by gas pressure, space charge or mass composition of ion beam or by configuration of ejecting electrodes. As it will be shown in the following description, the dual storage scheme is more flexible, allows full utilization of the ion beam and a number of automatic adjustments. More significantly the dual storage scheme generates an ion beam with a smaller phase-space and improves beam acceptance by the analyzer. The advantages of using an additional storage device will become apparent in the following detailed description of the preferred embodiment of the MR-TOF MS of the invention, which employs the dual storage scheme.

Fig. 7B briefly referenced above shows one example 61B of a gaseous continuous ESI ion source, comprising a spraying probe 62, a sampling nozzle 63, a sampling skimmer 64 and one or more pumps such as 65 and 75. The components and principles of operation of ESI ion sources are well described in the art. A solution of analyte compound is sprayed from the probe 62 in the region with atmospheric pressure. The highly charged aerosol evaporates forming gaseous ions of the analyte which are sampled via the sampling nozzle 63. The pump 65 evacuates the excessive gas to a gas pressure of a few mbar. The ions are further sampled via the sampling skimmer 64 with the assistance of the gas flow and electrostatic fields, generating a continuous ion beam 66, while gas is evacuated by a pump forming part of the ion guide 71.

Fig 7C shows one example 61C of a quasi-continuous gas-cooled MALDI ion source comprising a sample plate 67, a laser 68, a supply 69 of cooling gas, and a pump. The MALDI ion source 61B with the gas cooling generates ions of the analyte while illuminating a sample on a sample plate 67 by the pulsed laser 68. A supply 69 provides the cooling gas around the sample plate at an intermediate gas pressure of approximately 0.01mbar (WO9938185) or around 1mbar (WO0178106). Ions emitted from the sample plate are cooled and stabilized in gas collisions. Ion stability is a desired feature for the use in MR-TOF MS, since it employs a prolonged analysis time. The ion kinetic energy and the sharp timing characteristics will be dampened by the gas collisions. The resulting ion beam 66 is considered more of a quasi-continuous ion beam, rather than a pulsed ion beam.

Fig. 7D schematically illustrates one example of an intermediate ion storing guide 71. Both of the earlier described ion sources 61B and 61C are connected to the ion guide 71. The particular example 71 of the ion guide may comprise quadrupole rods 72 supplied with a radio frequency (RF) voltage, a set of supplementary electrodes 73, an exit aperture 74, and a pump 75. Note that the ion guide employs the same pump 75, as been referred in description of ion sources.

Components and principles of operation of both ion sources have been described. In the particular example illustrated as 61A having an ESI ion source, a continuous ion beam 66 is sampled via skimmer 64. With respect to the MALDI ion source 61B with gas cooling, a quasi-continuous ion beam is sampled via skimmer 64 – in both cases into the region with a gas pressure of few mTorr.

In the present invention, either a continuous or quasi-continuous ion beam 66 is directed into the ion guide 71. Ions are sampled via an aperture 64 while the pump 75 evacuates any excessive gas. The aperture 64 and the pump 75 may be similar in the case of both of the ion sources because of the approximate equal gas pressure in front of the aperture 64. The sampled ions are accumulated between the RF rods 72 while being dampened by the gas collisions and retarded by apertures 64 and 74. The ions are preferably confined close to axis of RF quadrupole and at or near the lower end of DC potential range. Periodically ion packets 76 are pulse ejected from the storing ion guide and into the accelerator 91, either directly or via an optional second ion storage device 81.

The invention may use ion storing where supplementary electrodes such as 73 organize axial DC distribution in the ion guide 71. The electrodes 73 preferably surround the RF rods 72 such that their electrostatic field efficiently penetrates between the rods. The axial DC distribution may be adjusted and varied in time to provide spatially-distributed ion storage, a controlled percentage of ion sampling, and a moderate duration of the ion ejection process.

Note that manipulations of the voltages on the supplementary electrodes 73 do not require any manipulations of the RF potentials on the RF rods 72. In fact it is considered advantageous to keep the RF voltage applied to the rods 72 in a steady state thus, providing a better focused pulsed ion packets. Since ions are ejected along the axis where the RF field is negligible, the RF field has very little effect on the axial ion velocity.

The storing ion guide 71 may be coupled directly to the accelerator 91 and preferably in an orthogonal orientation. Since the ion guide is filled with a gas it is preferable to use a soft ion ejection by employing small modulation of the potentials on the electrodes 73 and 74. Such slow (one to few tens of electron Volts) and fairly long (several microseconds) ion packets are compatible with the synchronized orthogonal acceleration. The scheme is not shown since it is fairly common practice (See e.g. US 6,020,586). The ion packet 76 passes via an additional differential pumping stage within the gas-filled ion guide to the analyzer at deep vacuum. The additional stage may comprise a lens, forming a nearly parallel ion beam. The ion packet enters the orthogonal accelerator 91, synchronously injecting ions into the analyzer. The orthogonal accelerator may be positioned either in the drift space of the MR-TOF analyzer of the invention, combined with one of the mirrors (or a pulsed portion of one ion mirror) of the planar MR-TOF analyzer and operated in a pulsed manner, or as a pulsed extension of the DC field of one the ion mirrors of the invention. The storage ion guide provides an advantage of improving the duty cycle of the orthogonal acceleration at the expense of ion mass range.

Fig. 7C illustrates one example of the second storage-device 81. The second storage-device 81 may be comprised of a generic ion trap 82, an exit aperture, either axial 88 or orthogonal 86, and a pump 85. The storage device 81 is connected to the ion guide 71, and preferably to a storage ion guide. Here the ions are continuously or pulsed-injected from the ion guide 71 into the generic trap 82. The generic ion trap 82 may be a 3-D ion trap, a linear ion trap formed in quadrupole, a multipole, or wire ion guide, preferably equipped with supplementary DC electrodes, RF channel, ring electrode trap, ion funnel or a combination of those devices. The trap is preferably maintained at a reduced gas pressure of about 0.1mTorr with the gas evacuated by the pump 85. Because of the combined action of the RF and DC fields, and by the gas dampening, ions are confined near the exit of the trap. Ions are then periodically ejected from the storage device 82 directly into the MR-TOF analyzer, either axially 87 or orthogonally 89, via a corresponding aperture such as 86 or 88 and serving to reduce the gas-load on the pumping system of the MR-TOF analyzer. Two schemes are shown on the fig 7C. The scheme at the left of the figure corresponds to direct ion ejection from the storage device 82 into the MR-TOF analyzer, either axially 87 or orthogonal 89. The scheme on the right side of the page corresponds to ion ejection using an optional accelerator 91, either axial 94

or orthogonal 93. A significant function of the additional storing device 81 is to prepare an ion cloud at different conditions compared to the rest of the ions stored in the first storing ion guide 71. Such conditions may differ by gas pressure, space charge of the ion beam, or the configuration of the ejecting electrodes. As will be shown in the following description, the dual storage scheme is more flexible, allowing full utilization of the ion beam and a number of automatic adjustments. Significantly it generates an ion beam having a smaller phase space and improves beam acceptance by the analyzer. The advantages of using an additional storage device will become apparent in the following detailed description of the preferred embodiment of the MR-TOF MS which employs the dual storage scheme.

Fig.9 illustrates a block diagram of a dual ion storage device using axial ejection and having an optional accelerator. The optional accelerator 91 may comprise a set of electrodes 92 located in the housing 97 which is evacuated by a pump 95. In the example shown in Fig. 9, the accelerator shares a housing and pump with the MR-TOF though they may be pumped differentially to enhance vacuum in MR-TOF. The pulsed ion beam 89 from the second storage device 81 is accelerated within a set of electrodes 92. There are many different types of accelerators described in the art. One example may be electrodes made of wires, rings or plates with slits or with meshes. They also may be comprised of electrodes supplied by an RF signal to confine the ion beam. The ions are accelerated either axially 94 or orthogonally 93 to the direction of the ion injection. The accelerator operates either continuously or in a pulsed-mode synchronized with ion injection. In all cases the accelerator may be arranged and controlled such that the ion package will experience a local compression 96 at some intermediate time-focusing plane, called an object plane.

Fig.10 shows one arrangement 101 of a second storage device 81 using pulsed axial ion ejection. The second storage device 81 may be comprised of a set of multipole rods 102 with short rod extensions 103 and an exit aperture 104. The storage device 81 may further communicate with an axial DC accelerator 91 which is comprised of DC accelerating electrodes 105 and an aperture 106.

In operation, the ions are formed in the ion source and preferably pass through an intermediate ion guide 71, either as a continuous ion source or as a slow ion packet. The second storage device 81 is preferably held at relatively low gas pressure on the order of 0.1mTorr to 1mTorr and sufficient for ion collisional dampening during a 1ms storage time. The rod extensions 103 may be supplied with the same RF signal as the rods 102, but kept at a slightly reduced DC (10-50V lower compared to rods 102). Ions are periodically stored and pulse ejected from the second storage device 81 by varying the potential on the exit aperture 104. At the ion storage stage, the aperture 104 is kept at a retarding potential thus forming a local DC-

well in the vicinity of the exit aperture 103 while still confining ions in a radial direction of the RF field produced by the of rod extensions. The sharpness of the DC-well may be adjusted such that the ion cloud size is approximately 0.5 to 1mm. At the ion ejection stage, the aperture 104 may be drawn to a strongly negative potential (for positive ions) to extract the ions along the axis and from the second storage device 81. Note that the RF field stays on. Since the ions are preferably confined near the axis they experience very little effect from the RF field during axial ejection. The DC accelerating electrodes 105 may serve as an energy corrector and a lens for the simultaneous spatial focusing of the ion packets 107. The exit aperture 106 may be used to reduce the gas load on the MR TOF MS pumping system. Estimates suggest that unless the ion cloud would create a space-charge potential of about 0.5V or greater, the parameters of the ion packets 107 are well suitable for MR-TOF MS. At a 0.2eV energy spread, an ion cloud diameter of 0.5mm, an acceleration potential of 5kV and a 500V/mm extraction field, the ion-beam parameters have a divergence below 1 degree, an energy spread below 5% and the turn-around-time of 1kDa ions below 8ns.

Fig. 11 illustrates one arrangement of orthogonal ion acceleration from a non-storing ion guide. The arrangement comprises an ion trap 108, a non-storing ion guide 109, and a DC accelerator 91. The arrangement 111 could be implemented with various types of ion traps and ion guides. The particular ion trap 108 of Fig.11 may be formed by an RF multipole set 112 surrounded by DC electrodes 113 and an exit aperture 114. A particular non-storing ion guide 109 may be comprised of a multipole set 115 having a slit 117 in one or more of the electrodes or an opening between the electrodes of the RF multipole. The multipole 115 may optionally be surrounded by supplementary DC electrodes 116. Both stages of the ion trap and the ion guide are preferably under vacuum by pumps 85 and 95.

In operation the ions are formed in an ion source and preferably come via an intermediate ion guide 71 either continuously or as a slow ion packet. The ion trap 108 may be held at a relatively low gas pressure of approximately 0.1-1.0 mTorr and sufficient for ion collisional dampening during 1ms storage times. The ions may be periodically stored and pulse ejected from the ion trap 108 as a slow ion packet (1-10us) by modulating potentials of DC electrodes 113 and of exit aperture 114. The multipole 115 of the ion guide 109 is supplied with a RF signal to continue radial ion confinement of the axially propagating ion packet. With some predetermined delay to the ion injection pulse, a second extraction pulse is applied to multipole rods 115. An optional pulse may also be applied to supplementary electrodes 116. The potentials on the multipole electrodes 115 are zeroed at a predetermined phase of the RF signal (say, for example, at zero volts) and then (after a brief delay of approximately between 10-300ns) switched to some predetermined pulsed potentials to provide ion bunching and ion

extraction in-between the multipole rods or through the slot 117 in one of the rods. The ions then undergo acceleration in the DC stage 91 and enter the MR-TOF MS 31. The delay between the first pulse ejecting ions from the ion trap 108 and the second extraction pulses in the ion guide 109 may be adjusted to maximize the mass range of the orthogonally extracted ions.

It should be noted that the storage device and the accelerator described above could be combined in a single unit. In addition the gas could be provided along the entire length of the rods 112 and 115. Moreover the aperture 114 and electrodes 113 could be omitted altogether and the electrodes 112 and 115 could be optionally combined into a single set of electrodes.

Fig.12 shows yet another embodiment of the storage device 121 referred to herein as 'a hybrid ion guide with 3D ion trap'. Referring to drawing figure, the storage device 121 comprises a quadrupole ion guide formed by two pairs of electrodes 122 and 123 and a 3-D Paul trap comprising a ring electrode 127 and cap electrodes 126 and 129. The ring electrode 127 is preferably open with a large-size aperture 125. The cap electrode 129 preferably includes an aperture 130 for orthogonal ion ejection.

In operation, a continuous radio frequency (RF) field spans across the ion guide 122, 123 and the 3-D trap 126,127, 128. In the simplest mode, the pair of electrodes 122 is connected to the ring electrode 127 to form one pole supplied with an RF voltage, while the pair of electrodes 123 is connected to the cap electrodes 126 and 129 to form the opposite pole. The same RF field may be achieved if the RF voltage is supplied symmetrically between the two poles. In a preferred mode a similar structure for the RF field is preserved. However, corresponding electrodes may be supplied with signal having the same frequency and phase, while having different RF voltage amplitudes and separately controlled DC potentials. The ions are supplied (continuously or pulsed) through the ion guide between the pairs of electrodes 122 and 123 and into the 3-D trap via an opening 125.

Distribution of RF and DC potentials form a mass dependent axial barrier between the linear quadrupole 122-123 and the quadrupole trap 126-129 with amplitude in the range of several volts, and in inverse proportion to the ion mass-to-charge ratio m/z. In general, the barrier causes ion sharing between the guide and the 3-D trap. By raising the DC offset the on electrodes 122-123 and with the assistance of gas collisions, a majority of the ions could be concentrated in the middle of 3-D trap. In a preferred mode the DC offset may be slowly ramped-up such that the barrier disappears for ions above some m/z*. Ions of m/z* pass over the barrier with a minimum amplitude of secular oscillations in the trap. Slow DC ramping allows a soft transfer of all ions into the trap. At the same time, ions coming from the ion source could be stored in the intermediate storing ion guide 71 to improve the duty cycle. After the ions are dampened in the 3-D trap (1-5 ms), the RF field could be switched off and after a

short and optimized delay (approximately 10-300 ns), a high-voltage pulse may be supplied to at least some of 3-D trap electrodes 126, 127 and 129, to eject an ion packet through the aperture 130 in the cap electrode 129. In another mode, the RF voltage may be replaced with a square-wave signal and the ion ejection pulse may be synchronized to a specific phase of the square wave signal such that the potential distribution stays constant during the ion ejection phase.

Fig.13 shows a segmented analog 131 of the hybrid trap 121. The pair of quadrupole rods 122 is replaced by a plate 132 with a channel 135. The ring electrode 127 is replaced by a plate electrode 137 with a circular hole 138. The pair of electrodes 123 is replaced by plates 133 and 134 symmetrically surrounding plate 132. The cap electrode 126 is replaced by a cap plate 136 and the cap electrode 129 with aperture 130 is replaced by a cap plate 139 having an aperture 140. Cap plates 136 and 139 are located parallel to plates 133 and 134 or as their extension. The plates are arranged as a sandwich shown on the left portion of Fig 13. The same electrodes are shown separately on the right part of Fig. 13.

In operation, the segmented trap 131 provides the same field structure in the vicinity of axis. It is a quadrupolar 2-D field near the axis of the channel 135 and a 3D-quadrupolar field near the center of the circular hole 138. The trapping field is formed by either an RF voltage or square-wave signal applied to the plates. The RF field provides ion sharing between the segmented ion guides and the segmented 3-D ion trap. Periodically the RF signal is switched off at some fixed phase of the RF signal (preferably 0V) and after a predetermined delay (approximately 10-300ns), a high-voltage pulse is applied to the electrodes to provide ion ejection within a nearly homogeneous electric field. The ion packet is extracted through aperture 140 which is also serving to reduce the gas load on the pumping system of the MRTOF. Preferably an RF signal is applied only to the central plates 135 and 137, a DC ramp applied to plates 133 and 134 (or including 132), and high voltage pulses applied to plates 136 and 140. Such an arrangement allows separation of the RF and DC signals and the high voltage pulses.

Other embodiments or method of ion storage such as shown by numeral 91 may include a linear ion trap formed by coaxial apertures (see e.g. A. Luca, S. Schlemmer, I. Cermak, D. Gerlich, Rev. Sci. Instrum., 72 (2001), 2900-2908), a segmented trap with orthogonal ejection (similar to that in US6670606B1), a segmented ring ion trap (Q. Ji, M. Davenport, C. Enke, J. Holland, J. American Soc. Mass Spectrom, 7, 1996, 1009-1017), a wire trap, and traps formed by meshes surrounded by electrodes with RF signals, helical wire traps, etc.

Fig.14 schematically shows a preferred embodiment of the MR-TOF MS 141 of the invention. The device 141 of the invention comprises a multi-reflecting analyzer 31 and a pulsed ion source 51. As earlier described the pulsed-ion source 51 comprises a sequentially connected continuous ion source 61, an intermediate storing ion guide 71, a second storing ion

guide 81 and an accelerator. Each main component may be formed by the one or more of the earlier described elements. The particular embodiment shown is an example of a continuous ion source 61 or ESI ion source, comprising a spray probe 62, a sampling nozzle 63, a sampling skimmer 64 and a pump 65. The intermediate storing ion guide 71 comprises a set of quadrupole RF rods 72, surrounded by supplementary pulsed electrodes 73, an exit aperture 74 and a pump 75. The second storing ion guide 81 comprise a gas confining cap 82, a set 83 of quadrupole RF rods, surrounded by a set 84 of supplementary pulsed electrodes, an exit aperture 88, and a pump 85. The accelerator 91 comprises a set of electrodes 92, a housing 97 shared with the MR-TOF MS analyzer and a pump 95. The MR-TOF analyzer 31 comprises a field free region 14, two planar and gridless ion mirrors 15, an in-line ion detector 34, a set of periodic lenses 17, a set 32 of entrance steering plates, and a set 33 of exit steering plates.

In operation, the ESI ion source 61 generates the continuous ion beam 66, which is stored in the storing ion guide 71 at an intermediate gas pressure (from approximately 0.01 to 0.1mbar). The intermediate storing ion guide 71 periodically ejects slow ion packets into the second storing ion guide 81, which operates at a lower gas pressure (from approximately 10^{-4} to 10^{-3} mbar). A gas confining cap 82 allows for a higher gas pressure in the upstream area of the second ion guide 81, thus improving ion dampening and ion trapping at a smaller gas pressure near the exit of the guide. This helps to reduce the gas load on the pump 95 and, thus, helps keeping the gas pressure lower in the chamber 97 of MR-TOF analyzer 31 and accelerator 91 (below 10^{-7} mbar) because of the extended flight path, compared to conventional TOF MS.

The slow ion packet contains a fixed portion of all ions accumulated in the first ion guide 71. As an example, approximately ten percent (10%) of the stored ions are sampled through the aperture 74 approximately every millisecond (1 ms). The balance between coming and leaving ions allows refreshing of the ion content every ten milliseconds. The amount of the ions stored in the first ion guide 71 depends on the intensity of ESI in the beam. At a typical ion flow of $3x10^8$ ions a second, the first ion guide 71 would contain about $3x10^6$ ions known to build up a noticeable space charge field. With only ten percent of the ions being sampled in the second storage, there are about 3.10^5 ions. Such ion cloud stored in $1mm^3$ volume would create about 30meV potential of space charge field which is close to the thermal energy (gas kinetic energy of 25meV) and moderately affecting ion initial parameters.

The dual storage scheme provides several advantages. First, pulsed injection into the second storing quadrupole ensures a complete ion dampening at low gas pressure. Second, the amplitude of the RF signal in the first quadrupole section may be adjusted to operate as a low mass filter. By removing most of the solvent ions and the chemical background ions, the space charge is further reduced. Third, by using selective excitation of the secular ion motion one can

also achieve a selective removal of the most intense ion species, building-up space charge and saturating the detector. Besides, by adjusting the duration of the ion injection one can control the intensity of the ion beam. It helps to improve the dynamic range of the data acquisition and in avoiding saturation of the detector.

The first ion guide 71 ejects slow ion packets by a very gentle pulsed axial field, generated with the assistance of the pulse potentials on the exit aperture 74 and optionally on the additional electrodes 73. The use of the set 73 of additional electrodes allows an accurate control of the energy and the amount of ejected ions within the packet. The ejected ion packet is almost completely trapped in the second storing ion guide 81, using a pulsed trapping scheme. In more details, a potential on exit aperture 88 forms a repelling DC barrier while the RF field of the electrodes 83 confine ions in the radial direction. Ion packet gets reflected from the far end 88, however, by the time the ions return to the entrance (74) of the second guide 81, they will see a repelling potential of electrode 74 which was raised after the completion of the ion ejection from the first ion guide 71. Ion kinetic dampening is accelerated because of a higher gas-pressure in the beginning of the ion guide 83. The local increase of gas pressure is formed by the gas confining cap 82 and by a gas jet emerging from the aperture 74.

Trapped ions get confined in the DC potential-well formed by the additional electrodes 84. These electrodes surround the RF rods 83 of the second ion guide 81 to make an effective and symmetric penetration of the potentials of the additional electrodes. Referring to the electrostatic field on the axis of the ion guide 81, a set of additional electrodes 84 forms an axial distribution of the DC field while generating a moderate octapole DC field in the radial direction. It is important to keep such octapole DC-field small enough to avoid ion instability during long term storage. As a numeric example, an RF potential of 1.5kV and a frequency of 3MHz is applied to 5mm quadrupole rods positioned at 15 mm between centers to allow 5 mm inscribed diameter. Each additional electrode is formed as a plate having a central hole of 5mm and 7mm holes for rods. About twenty percent of the potential on each plate penetrates to the center of the quadrupole assembly. Three plates are located 3mm apart from each other and 5mm away from the exit aperture. By applying a 10V drop to the central plate we form a DC well of about c.a. 2V deep. Ions with energy of 100meV are confined to a cloud of c.a. 1mm long and a fraction of mm in diameter. The arrangement has very little effect on the ion stability and allows the storing of ions within at least one decade of mass to charge (m/z) ratio.

After collisional dampening and confinement in the ion guide 81, the ion packet is axially ejected (in the X direction) into the DC accelerator 92 and then into the MR-TOF analyzer 31. After emptying the second storage the pulsed potentials are returned to their trapping state to prepare for the next cycle of ion storage. The pulsed ejection is made with the

aid of high voltage electric pulses, applied to the set 84 of additional electrodes and to the exit aperture 88, while keeping RF potentials unchanged. Low gas pressure in the second storing quadrupole 81 helps to avoid gas discharges while applying high voltage pulses. Since all the ions are stored in a small volume, the pulses should not spoil any other ions and the pulse amplitude could be fairly high -- enough to noticeably reduce the ion turn-around-time. Thus, the ability to compress the ion packet into a small cloud and to apply high-voltage accelerating pulses are, in fact, significant reasons for the dual storage arrangement. The ion packet parameters may not otherwise be achieved when ejecting quickly directly from the first ion guide 71.

Application of fairly large, ejecting pulses causes a substantial reduction of the ion turn-around-time and thus allows using an ion guide directly for MR-TOF MS. In our ion optics simulations, made for the above geometrical example, we found that by applying high voltage pulses to the additional electrodes the turn-around-time could be reduced to few nanoseconds. For example, by applying a 5kV pulse to the middle additional electrode (out of three) and a –1kV pulse to exit aperture, an axial field reaches c.a. 200V/mm. Assuming a 200meV initial energy spread and a 1mm size of the stored ion cloud, the turn-around-time of 1000amu ions is 10ns only, and the energy spread of the ejected ion packets is below 200eV. By applying a c.a. 4kV DC post - acceleration in the DC accelerator 92, the ion beam has less than a 5% energy spread, is well focused, and has a phase space below 10π*mm*mrad which is compatible with the wide acceptance and high order time-of-flight focusing of the MR-TOF analyzer of the invention.

In ion optics simulations by the inventors the resolution of the MR-TOF MS appears to be mostly limited by turn-around-time. As a numerical example, ions of 1000amu, accelerated to a 4keV energy and a velocity of 3×10^4 m/s have a turn-around-time of 10ns while having a 1ms flight time in 0.25m wide analyzer with 50 reflections (25 reflections while shifting in one direction and 25 reflections on the way back). Such an analyzer provides a folded path with the effective flight path of 30m. If a 10ns turn-around-time is indeed the only limiting factor, then resolution reaches approximately R=50,000. Further extension of the flight time is expected to improve resolution even more. A longer accumulation would cause some deterioration of the turn-around-time. However, the increase of the space charge field and of the turn-around-time is expected to be slower than the increase of flight time.

Increasing storage time stresses the dynamic range of the detector. With an increased time-of-flight in MR-TOF and more efficient ion utilization, ions from up to 1 ms accumulation arrive to detector in short packets of 10-20 ns duration. To avoid saturation of the detector and therefore loss of analytical parameters (such as mass accuracy, mass resolution, dynamic range,

etc.), one may enhance dynamic range of the detector by using a secondary electron multiplier (SEM) combined with an analog-to-digital converter (ADC) rather than with a micro-channel plate detector (MCP) combined with a time-to-digital converter (TDC). As one of embodiments, a hybrid detector could be employed, wherein a single micro-channel or micro-sphere plate is followed by a scintillator and photomultiplier. It is also proposed to use any combination of the following measures: a) using SEM with two collectors sampling electrons at different stages of amplification or b) using an arrangement with a dual SEM combined with a rapid steering device and/or c) using dual amplifiers connected to a pair of acquisition channels and/or d) alternating between two different storage time in the intermediate or second storing trap such that the intensity of the ion pulses varies between shots. Note that MR-TOF is expected to have longer ion pulses (10-20ns), compared to conventional TOF (1-3ns). Lower bandwidth requirements make it easier to implement the means mentioned above.

Higher use efficiency of the ion in MR-TOF would cause faster aging of the detector. In order to increase the life time of the detector and to enhance its dynamic range, it is also proposed to use a pre-scan of the mass spectrum at lowered storage times. From this pre-scan, a list of exceedingly intense peaks could be deduced and stored in the memory of the instrument controller. This list could be used to control a pulsed ion selector. The pulsed ion selector could be incorporated in the detector or any of the deflectors or lenses or in the drift space of MR-TOF in any of the above embodiments. This selector is used to suppress ions with mass-to-charge ratios corresponding to the intense ion peaks by deflecting or scattering a substantial portion of the intense packets while they fly through the selector. It is also possible to divert these peaks to another detector with a substantially lower gain. Preferred embodiments of the selector include: a Bradbury-Nielsen ion gate, a parallel-plate deflector, a control grid within the ion detector (e.g. a grid between dynodes or microchannel plates pulsed to stop passage of secondary electrons through it). Suppression of ion intensity may be considered in the calculation of actual ion intensity. The number of ions per shot may be suppressed at any stage of ion storage or at the MR-TOF or at the detector.

In addition to stressing and aging the detector, an excessive amount of ions per pulse (above $2*10^5$) is responsible for build-up of a space charge in the storage devices. Various strategies may include a controlled suppression of the ion beam intensity or a number of the ions per pulse at stages of preliminary or secondary ion storage. Such controlled suppression may include a selection of the mass range of interest, removal of low mass ions, and mass selective removal of the most intense ion components, for example, by exciting their secular motion in a RF trapping device and causing selective loss of those ions.

The above-described scheme of MR-TOF MS combined with ion trap source allows one hundred percent (100%) conversion of the continuous ion beam into ion packets. Besides, achievable parameters of ion packets allow a complete transmission of the ions through the novel MR-TOF MS, and if turn-around-time is the major limiting factor, then it still allows reaching resolution of 50,000 within a 1m long instrument. Those parameters exceed the resolution and the sensitivity of existing o-TOF MS and is far superior to the parameters of the existing MR-TOF MS

Stable ion confinement in the multi-reflecting analyzer and within a set of periodic lenses improves sensitivity and resolution of the MR-TOF and allows a prolonged ion separation. Those properties of novel analyzer could be very useful in a tandem mass spectrometer with parallel MS-MS analysis described in a co-pending published application WO2004008481, the contents of which are incorporated by reference. There we introduce a set of periodic lenses into a first multiple reflecting analyzer of a tandem TOF, thus improving both sensitivity and resolution of the parallel MS-MS analysis.

Referring to Fig. 15, a preferred embodiment of the tandem mass spectrometer 151 comprises a pulsed ion source 51, a multi-reflecting mass spectrometer 31, a fragmentation cell 152 and an orthogonal time-of-flight mass spectrometer 161. The pulsed ion source 51 comprises a continuous ion source, a dual storing ion guide and an accelerator. The second storing ion guide is shown here as an RF linear ion trap 83 with auxiliary DC electrodes 84, set up for axial ion ejection. The above described MR-TOF MS 31 comprises a field-free region 14, an off-line detector 34, two planar gridless mirrors 15 preferably containing more than four electrodes, adapted to provide high order time-flight and spatial focusing, a set of periodic lenses 17 for stable ion confinement along the folded ion path, and a pair of edge deflectors 32 and 33, preferably incorporated into edge elements of periodic lenses 17 and providing extension of flight path by edge ion reflections.

The fragmentation cell 152 is a fast fragmentation cell described in detail in the referenced co-pending patent application. Preferably the fragmentation cell comprises a short (5-30mm) RF quadrupole 158 for radial ion confinement, as well as auxiliary DC electrodes 159 and an exit aperture 160 to form a time dependent axial electric field. The quadrupole is surrounded by an inner cell 156, filled with gas at a relatively high gas pressure (.1-1Torr) via port 157. To reduce the gas load on the MR-TOF, the space around the cell 156 is pumped by a turbo pump 155. To enhance ion transmission, the inner cell is supplied with focusing lenses 154 on both ends.

The orthogonal TOF 161 is a conventional device, well described in the art. It comprises an orthogonal acceleration stage 163 with a pulsing electrode 162 and an in-line

detector 164, a pump 165, an electrically floated field free region 166, an ion mirror 167 and a TOF ion detector 168. The orthogonal acceleration is preferably made of flat electrodes with slits oriented along the entering ion beam. The orthogonal TOF differs from most conventional instruments by a shorter ion path (approximately 0.3-0.5m) and by a higher acceleration voltage (above 5kV) to provide for a fast fragment analysis of about 10us time.

In operation, pulsed ion source 51 periodically (say, once per 10ms) generates bursts of parent ions, converting a continuous ion flux from the ion source 61 into ion pulses by storing and ejecting ions from the second storage device 82. The mixture of the parent ions having different mass-to-charge (m/z) ratios represents a mixture of different analyzed species. The ions are separated in time in the first analyzer 31 with an extended multiple-folded ion path exceeding 30m. The analyzer operates at reduced ion energy of about 50 to 100eV to extend separation time to about 10ms. The MR-TOF of the present invention is very well suited for ion separation at reduced energies and prolonged flight times. The analyzer tolerates relatively high energy spread (up to 20%) by providing a high order time-of-flight focusing with respect to the ion energy. It also provides an exceptional transmission at reduced ion energies. Ions are bounced in X-direction and periodically focused in the Z-direction by ion mirrors. Simultaneously, ions are retained along the jig-saw folded trajectory because of the periodic focusing in a set of periodic lenses 17, thus providing periodic focusing in the Y-direction. The ion flight path is extended by reflections in the edge deflector 33. Initially injected ions follow path 35. After steering in the edge deflector 32, ions follow trajectory 36 and experience multiple bounces between mirrors. The trajectory 36 approaches the second edge deflector 33 from the right. The edge deflector 33 steers ions such that they follow trajectory 37. Such steering reverses the direction of ion drift along the Y-axis. The trajectory 37 again passes through the multiple lenses and approaches the edge deflector 32 from the left. The static edge deflector 32 steers the beam into the fragmentation cell 152. Note that the ion edge reflection is made using constant voltages. The flight path is doubled while retaining full mass-range of the analyzer.

The deflectors could be used in a pulsed mode for several purposes. A further extension of the flight path is possible at the expense of the mass range. By pulse adjusting deflector 32 to a double-deflecting voltage the trajectory becomes enclosed. Ions coming along the trajectory 37 will be returned back into the trajectory 36 and will experience multiple edge-deflections until the deflector 32 is switched back to a smaller deflection and the ions are released along the trajectory 39 or trajectory 38 in case deflector 32 is switched off to divert ions onto the off-line detector 34. Diversion onto the detector 34 may be used after a single edge deflection for acquiring the mass spectra of the parent ions. The deflector 32 is switched off

after the heaviest ions of the trajectory 35 pass through the deflector into the MR-TOF and before the lightest ions of the trajectory 37 approach the deflector 32. To bypass the analyzer by steering the beam from trajectory 35 into the off-line detector 34 results in a crude mass separation or suppression of unwanted species, like low mass or very intense ions.

Parent ions are introduced into the fragmentation cell 152 at a kinetic energy (about 50 to 100eV) sufficiently high for ion decomposition. As described in the published co-pending application, the fragmentation cell is filled with gas, preferably at an elevated gas pressure above 0.1 Torr, and the cell is kept short (about 1cm). A higher (greater than 0.005 to 0.01Torr) gas pressure in the cell requires an additional envelope of differential pumping with additional means of ion focusing either electrostatic lenses or an RF focusing devices. Ion transfer through the cell is accelerated by the axial DC field or a moving-wave axial field. As a result, ions pass the cell in about 20 μs time, while spreading the ion packet by less than 10us. The same field allows periodic storing and pulse ejection of the ions, or at least a substantial synchronous modulation of the ion velocities.

Fragment ions are then ejected from the cell and into the second TOF analyzer 161 for mass analysis. To improve the efficiency of the second analyzer, ions are periodically bunched together about every 10μs at the exit of the fragmentation cell 152 and those pulses are synchronized with pulses of the orthogonal acceleration 163 in O-TOF 161. The second analyzer 161 is adjusted to have a short flight time (10 to 30μs), which is expected to be achieved at a moderate flight path (less than 1m) and high ion energies (above 5kV). Drastically different time scales of the two analyzers (at least 2 orders of magnitude) allow parallel MS-MS analysis of all parent ions. Fragments of different parent species are formed at a different time and a so-called time-nested data acquisition system is used to record separate fragment mass spectra without mixing them together.

Note that in general the fragmentation cell may incorporate any RF storing device described in the art or in the present invention. By using storing and periodic pulse ejection of the cell one may equally well employ any other type of TOF MS, as long as it has short separation time, around 10μs. For example, another MR-TOF MS may be used as a second TOF analyzer, particularly if acceleration voltage is raised higher (say 5kV) and flight path is adjusted short by using shift ion reflection.

The described MS-MS instrument is expected to have an extremely high throughput of MS-MS analysis (up to hundreds MS-MS spectra a second), particularly valuable in combination with on-line separation techniques. Such tandem MS are expected to be applied for analysis of extremely complex mixtures, like combinatorial libraries in pharmaceutical studies or peptide mixtures in proteome studies. The instrument has a limited mass resolving-power

(resolution) at both stages of mass analysis. Assuming a 1ns time resolution of the TOF2 data system and a 10ms separation time in the TOF1, the product of the two mass resolving powers R1 * R2 is less than $2.5*10^6$, e.g. making a powerful analytical combination where R1 is approximately equal to 300-500 and R2 is approximately equal to 3000-5000, and considering capabilities of parallel MS-MS analysis. Note that R1>300 is sufficient for separating between groups of isotopes of parent ions and R2>3000 is sufficient for charge state determination of moderate mass ions (m/z<2000 a.m.u.).

Resolution of both stages may be improved by using a larger separation time in TOF1. Stable retention of the ion beam in TOF1 would allow a much longer separation without loss in TOF1. Vacuum better than 10^{-11} Torr has been achieved in FTMS, allowing extension of flight time to minutes. However, a possibility of further extension of TOF1 separation time much beyond 10ms is somehow limited by the space charge effects in the pulsing ion trap. Space charge limit and limited storage time would not allow much higher resolution in both stages. As an example, the combination of R1=100,000 and R2=100,000 with a product $R1*R2=10^{10}$ would require at least 40 seconds storage time, storing about 10^{10} ions generated by the ESI source at such period. An ion cloud of about 1mm diameter would have space charge potential of about 10kV, and virtually impossible to trap at the time of this writing. There are numerous ways of reaching a compromise by limiting the number of ions in the trap below 10^6, limiting and controlling the ion injection time into a pulsing trap or by using a prior mass separation or by selective filtering of abundant ion species. Such ion preparation steps could be made either in the intermediate ion guide 71 or in the second storage device 81.

Higher resolution of both MS stages seems to be incompatible with parallel analysis, since it requires ion losses by attenuation of the entire beam (by limiting of injection time), separation of the desired species, or by filtering abundant species. However, it looks more promising to combine rapid screening at low resolution with subsequent data mining using very high resolution in both stages. First step allows the mass determination of the parent ions of interest, while the second analysis step is used for high precision and confident analysis of those species.

Fig. 16 illustrates a preferred embodiment of a high resolution tandem time-of-flight tandem mass spectrometer 171. The tandem 171 is similar to the above described tandem TOF-TOF 151, except for using timed ion selection in the first MR-TOF and using a second multi-reflecting analyzer 31B for the fragment analysis. The second MR-TOF analyzer 31B is somewhat similar to the first MR-TOF. It comprises a field-free region 14B, two pair of planar gridless mirrors 15B, a set of periodic lenses 17B, a detector 34B, and a pair of edge deflectors 32B and 33B. The second analyzer 31B also comprises an additional lens deflector 173

incorporated into the second lens of the periodic lens set 17B for the purpose of flight path adjustment.

Other elements of the tandem MS 171 are similar to the elements described above. The pulsed ion source 51 may comprise a continuous ion source, a dual storing ion guide, and an accelerator. The first MR-TOF MS 31A may comprise a field-free region 14A, two pair of planar gridless mirrors 15A, a set of periodic lenses 17A, a pair of edge deflectors 32A and 33A, an off-line detector 34A and also a timed ion selector 172 (not used in the second MR-TOF 31B). The fast fragmentation cell 152 may be comprised of a short (5-30mm) RF quadrupole 158 filled with gas at a relatively high gas pressure (0.1-1Torr) through port 157. The quadrupole may be surrounded by an inner cell 156 with a focusing lens 154 on both ends. The inner cell 156 preferably includes apparatus 159 and 160 for slowing and accelerating of the ion passage through the cell. One example of the apparatus 159, 160 is a system for modulating the axial DC field.

In operation, ions are stored in the pulsed-ion source 51 and are ejected into the first MR-TOF analyzer 31A for time-of-flight separation. Separated ions, or a portion of those ions, are admitted by the timed ion-gate 172 into the fragmentation cell 152, where the ions undergo fragmentation. Periodically the fragment ions are pulsed out from the fragmentation cell 152 into the second MR-TOF analyzer 31B for mass analysis. Described below are two modes of operation for the tandem MR-TOF– a high throughput mode of parallel MS-MS analysis and a high-resolution mode of sequential MS-MS analysis.

In the high throughput mode for the tandem MR-TOF, the first analyzer is operated at a reduced ion energy controlled by the potential of a floatable field free region 14A, adjusted to approximately –50V. Separation takes approximately 10ms and all parent ions are admitted into the fragmentation cell 152. The timed ion-gate 172 remains off while admitting the parent ions into the fragmentation cell 152, though could be used to suppress low mass range containing a majority of solvent and chemical background ions. The second analyzer may be adjusted to a high ion energy, controlled by the potential of the field free region 14B held approximately –5kV, i.e. the ion velocities are higher by one order of magnitude compared to the first analyzer. The flight path in the second analyzer is substantially reduced by using an additional deflector 173, reverting ion drift direction. The ions experience only two reflections by the ion mirrors 15B and are directed into the detector 34B. Typical flight path of the fragment ions becomes approximately 0.5m, i.e. almost 2 orders of magnitude shorter when compared to the first MR-TOF 31A. The time scales are different by almost 3 orders of magnitude, which allow the earlier described parallel MS-MS analysis of multiple parent ions with a time-nested data acquisition. Such analysis allows rapid allocation of the parent ions having a range of the

desired fragments (for example, for peptides composed of amino acids it is determined by the presence of the so-called immonium ions). The information on parent ion masses could be used for accelerating detailed MS-MS analysis in the second analysis mode with a higher resolution and higher specificity.

In the high resolution mode for the tandem MR-TOF, both analyzers are operated at an elevated energy and resolution. The energy is adjusted by applying a negative high voltage potential (say –5kV) to both field free regions 14A and 14B. At a typical flight path of approximately 30m, the flight time appears to be around 1ms. As a result, the frequency of a pulsed ion source needs to be adjusted to 1kHz. Extraction pulses in the second storage device are adjusted to provide for much stronger electric field, similar to those employed in a high resolution MR-TOF MS. Higher voltage pulses (say -5kV) are applied to the exit aperture 92 with corresponding positive high voltage pulses (+5kV) being applied to the auxiliary electrodes 84. A stronger electric field causes a proportional reduction of the turn-around-time (to approximately 5 to 10ns) and a proportional enlargement of the ion energy spread (100-200eV), estimated in a case of 0.5mm sized ion cloud. Expected resolution of the first MR-TOF analyzer is expected to be on the order of 50,000 to 100,000.

To select a single species of ions at such resolution, one would need 0.3mm spatial resolution of timed ion selector, reachable with a Bradbery-Nielsen gate – a device composed of two alternated rows of wires, located in one plane. By applying a short pulse between two rows (approximately between 10-30ns) a short pulse of ions is admitted through the gate while the other species are steered away and lost at a subsequent stop. As an example, a timed ion-gate is located near the first lens and in the plane of intermediate time-of-flight focusing. A 1000V pulse is applied to the steering wires to divert the ions by 3 degrees (1/20 mm) sufficient to miss the 1 mm entrance aperture 153 of the CID cell. The resolution of the parent ion selection may be further improved by using multiple edge reflections with a simultaneous extension of the flight path and flight time in the first MR-TOF. The associated shrinkage of the mass range is no longer important, since the gate admits one m/z of parent ions. In this situation it is also desirable to reduce the energy spread of the parent ions below 50eV at the cost of a larger turn-around time, which may be compensated by a longer flight path, lower acceleration energy, and a longer flight time in the first analyzer.

Mass selected parent ions are decelerated to about 50-100 eV and focused at the entrance aperture of the fragmentation cell 152. Injection at such energies causes fragmentation of the selected parent ions. The fragments are stored in the fragmentation cell 152 using RF confinement in the RF trap 157 and by arranging an axial DC well formed by DC potentials of auxiliary electrodes and of the exit aperture. By applying electric pulses to those electrodes, the

fragmented ions are pulse ejected into the second MR-TOF for mass analysis. The parameters of the ion pulse and of the second analyzer are similar to those in the first MR-TOF. The CID cell may incorporate various elements and schemes of the pulsed ion sources described earlier. Thus, mass analysis of the fragmented ions is expected at a high resolving power (resolution) of about 50,000 to 100,000. The described tandem MR-TOF allows 100% usage of the analysis time. While the fragment cell 152 is emptied and the fragmented ions are mass separated in the second MR-TOF 31B, the first analyzer 31A may be used simultaneously for selecting parent ions and injecting the selected parent ions into the fragmentation cell.

Fig. 17 shows an economy tandem instrument 181 comprising a pulsed ion source 51, a single MR-TOF analyzer 31, followed by a fragmentation cell 182 which traps ions and injects them back into the MR-TOF for subsequent mass analysis or separation. The instrument provides a high-resolution sequential MS-MS analysis or a multi-step MS^n sequential analysis, simply by repeating the steps of ions selection, fragmentation and reverse injection.

Multiple usage of the MR-TOF also requires minor adjustment of the deflection regimes in the MR-TOF. At a stage of the parent separation, both deflectors 32 and 33 stay on at constant steering potentials. The ions follow the sequence of trajectories 35, 36, 37 and 39. Timed ion-gate 172 admits the ions of interest into the cell along the trajectory 39. The ions are decelerated to about 50-100eV and undergo fragmentation. The ion fragments are stored by RF fields on the electrodes 187, a DC-trapping potential formed at the entrance aperture 184, auxiliary electrodes 188 and the back electrode 189. After a sufficient predetermined delay, the ions are collisionally dampened and are pulse ejected from the cell towards the MR-TOF. The ejected ions follow the reverted trajectory 39 before proceeding along trajectory 37. However, at about the time of ion ejection from the cell 182, the deflector 33 is switched into a different deflecting mode. The ions are steered at a half angle, bounce from the right mirror along the trajectory 190 and revert their motion along trajectory 37 and then 39. Then either deflector 32 is turned off to pass all of the ions onto the off-line detector 34 or timed ion selector 172 is used to select daughter ions of interest to pass them into the fragmentation cell for further steps of MS^n analysis.

The various embodiments described above are provided to illustrate the different implementations of the invention. Unless specifically indicated, the ranges and parameters are provided merely for the purposes of example, and are not intended to be limiting to any aspect of the invention. Further, it may be apparent to those skillful of the art, that numerous changes could be made while staying within the spirit and principle of the invention.

WE CLAIM:

CLAIMS

1. A multiple-reflecting time-of-flight mass spectrometer (MR TOF MS) comprising:

an ion source;

an ion receiver downstream from said ion source;

at least one ion mirror assembly intermediate said ion source and said ion receiver and elongated in a shift direction for improving sensitivity and resolution of the MR-TOF MS; and

a drift space intermediate said ion mirror assembly;

said ion source, ion receiver, ion mirror assembly and said drift space arranged to provide a folded ion-path between said ion source and said ion receiver composed of at least one reflection by said ion mirror assembly for separating ions in time according to their mass-to-charge ratio (m/z) so that a flight time of the ions is substantially independent of ion energy.

2. The MR-TOF MS as defined in claim 1, further comprising a lens assembly disposed within said drift space along said at least one shift direction and with a period in said shift direction corresponding to ion shift per integer number of ion reflections.

3. The MR-TOF as defined in claim 1, further comprising: a timed ion selector including one of a Bradbury-Nielsen ion gate, a parallel plate deflector, and a control grid within said ion detector.

4. The MR-TOF MS as defined in claim 1, wherein said ion source comprises one of an ion storage device and an ion accelerator.

5. The MR-TOF MS as defined in claim 1, wherein said ion source comprises a continuous ion source.

6. The MR-TOF MS as defined in claim 1, wherein said ion source comprises one of a SIMS, a MALDI, an IR-MALDI.

7. The MR-TOF MS as defined in claim 5, wherein said ion source comprises one of an ESI, an APCI, an APPI, an EI, a CI, a PI, an ICP, a gas-filled MALDI, an atmospheric MALDI, a gaseous ion reaction cell, a DC/field asymmetric ion mobility spectrometer, and a fragmentation cell.

8. The MR-TOF MS as defined in claim 1, wherein said ion receiver includes an ion detector having an extended dynamic range.

9. The MR-TOF MS as defined in claim 1, wherein said ion receiver comprises a gas-filled cell selected from one of a fragmentation cell, a molecular reaction cell, an ion

reaction cell, electron capture dissociation, ion capture dissociation, a soft deposition cell, a cell for surface ion dissociation,

10. The MR-TOF MS as defined in claim 1, wherein said ion mirror assembly comprises a plurality of electrodes shaped and spaced relative to one another to provide a spatial ion focusing and time-of-flight focusing of ions substantially independent ion energy and on ion position in a plane transverse to said ion path.

11. The MR-TOF MS as defined in claim 1, wherein said ion mirror assembly includes one of a parallel assembly of conductive square frames, slotted plates, bars, and rods, each having an optional edge termination.

12. The MR-TOF MS as defined in claim 1, wherein at least a portion of said ion mirror assembly is operably connected to a pulsed voltage supply for gating ions in or out of the MR-TOF MS.

13. The MR-TOF MS as defined in claim 1, wherein said ion mirror assembly comprises at least two electrodes having voltages of opposite polarities relative to the other to form an attractive lense.

14. The MR-TOF MS as defined in claim 1, wherein said drift space comprises an ion deflector connected to one of a DC voltage supply and a pulsed voltage supply.

15. The MR-TOF MS as defined in claim 1, wherein said lens assembly includes at least two lenses elongated transversely to said ion path.

16. The MR-TOF MS as defined in claim 4, wherein said ion storage device comprises a gas-filled set of electrodes having a radio-frequency (RF) voltage applied to at least one of said electrodes.

17. The MR-TOF MS as defined in claim 4, wherein said ion storage device comprises a plurality of sets of electrodes having a radio-frequency (RF) voltage applied to at least one electrode in a first set of electrodes and a pulse voltage applied to at least one electrode in a second set of electrodes.

18. The MR-TOF MS as defined in claim 4, wherein said ion accelerator comprises a pulsed orthogonal accelerator.

19. The MR-TOF MS as defined in claim 4, wherein said ion accelerator comprises a plurality of electrodes, each having a slit along said shift direction of the MR-TOF MS.

20. The MR-TOF MS as defined in claim 4, wherein said ion accelerator comprises one of a pulsed ion mirror assembly, and a pulsed portion of said ion mirror assembly.

21. The MR-TOF MS as defined in claim 4, wherein said ion accelerator comprises one with pulsed voltages, and an accelerator with static voltages.

22. The MR-TOF MS as defined in claim 5, wherein said continuous ion source comprises an intermediate ion storage guide preceding said ion storage device and having a gas pressure greater than said ion storage device.

23. The MR-TOF MS as defined in claim 5, wherein said continuous ion source comprises, at least two gas-filled sets of electrodes having a radio-frequency (RF) voltage applied to at least one set of said gas-filled electrodes.

24. The MR-TOF MS as defined in claim 8, wherein said ion detector comprises one of a secondary electron multiplier having at least one dynode, a scintillator and photomultiplier, a micro-channel, micro-sphere plates, at least two channels of detection, at least two anodes each connected to a data acquisition system having an analog-to-digital converter (ADC).

25. The MR-TOF MS as defined in claim 8, wherein said ion detector dynamic range is extended by alternating scans with various intensity of said pulsed ion source.

26. The MR-TOF MS as defined in claim 8, wherein said ion detector dynamic range is extended by alternating scans with varying duration of ion injection into an ion storage device.

27. The MR-TOF MS as defined in claim 9, wherein said gas-filled cell includes at least one electrode connected to a radio-frequency (RF) voltage for one of dampening ion kinetic energy in gas collisions, stabilizing internal ion energy, confining ions, fragmenting ios, selecting ion species and retaining ions for exposure to reactant particles.

28. The MR-TOF MS as defined in claim 14, wherein said ion deflector comprises at least one steering plate.

29. The MR-TOF MS as defined in claim 14, wherein said ion deflector is located on a far side of said shift axis opposite to said ion source for steering ions in a static mode to change direction of said ion path.

30. The MR-TOF MS as defined in claim 14, wherein said ion deflector is located on a similar side of said shift axis as said ion source for directing ions toward one of an off-axis detector, a MR-TOF analyzer, and revert in a direction of ion shift for a time of ion confinement within the MR-TOF MS.

31. The MR-TOF MS as defined in claim 16, wherein said gas-filled set of electrodes comprises at least one of an ion guide having a plurality of elongated rods, a 3-D quadrapole ion trap, a linear ion trap with ion ejection, an RF channel with at least one electrode having an opening for ion passage, a ring electrode trap, a hybrid ion guide with a 3-D ion trap, and a segmented analog of the aforementioned electrodes formed of at least two plates.

32. The MR-TOF MS as defined in claim 5, wherein said ion storage device includes one of a filter of ion components, a discriminator of ion components, and a suppressor of ion components.

33. A tandem time-of-flight mass spectrometer (MR-TOF MS), comprising:

a pulsed ion source;

an MR-TOF MS to separate parent ions;

a fragmentation cell downstream of said MR-TOF MS for fragmenting the parent ions into daughter ions; and

a mass spectrometer downstream of said fragmentation cell for detecting said daughter ions;

where said MR-TOF MS comprises an assembly of two grid-less and parallel ion mirrors separated by a drift space and substantially elongated in one shift-direction.

34. The MR-TOF MS of claim 33, further comprising an ion selector subsequent said fragmentation cell.

35. The mass spectrometer as defined in claim 33, wherein said fragmentation cell comprises a gas-filled cell having an differential pumping stage and an ion focusing device.

36. The mass spectrometer as defined in claim 33, wherein said fragmentation cell comprises an internal gas pressure P associated with a cell length L (P*L) above 0.2 Torr*cm.

37. The mass spectrometer as defined in claim 33, wherein said fragmentation cell comprises a gas pressure P>0.5 Torr and L< 1cm.

38. The mass spectrometer as defined in claim 33, wherein said fragmentation cell comprises a gas filled set of electrodes having a radio frequency (RF) voltage applied to at least one of said electrodes for confining ions in radial direction.

39. The mass spectrometer as defined in claim 33, wherein said fragmentation cell further comprises a set of electrodes connected to one of a DC and slow-varying voltage to form an axial DC electric field, and an axial moving-wave electric field to control velocity of ion motion in said fragmentation cell, said DC voltage being applied to one of: the same set of electrodes and a dissimilar set of electrodes.

40. The mass spectrometer as defined in claim 33, wherein said mass spectrometer downstream of said fragmentation cell comprises a time-of-flight mass spectrometer (TOF MS).

41. The mass spectrometer as defined in claim 40, wherein said TOF MS comprises an orthogonal ion accelerator.

42. The mass spectrometer as defined in claim 40, wherein said TOF MS comprises ion path less than, and an acceleration voltage greater than in said MR-TOF MS to produce an ion flight time in said TOF MS at least 100-fold less than in said MR-TOF MS.

43. The mass spectrometer as defined in claim 40, wherein said TOF MS comprises a data system adapted for parallel acquisition of daughter spectra without mixing spectra corresponding to different parent ions.

44. The mass spectrometer as defined in claim 40, wherein said TOF MS includes a first and a second multi-reflecting time-of-flight mass spectrometer (MR-TOF MS).

45. The mass spectrometer as defined in claim 44; wherein said second MR-TOF MS is substantially identical in construction to said first MR-TOF MS.

46. The mass spectrometer as defined in claim 41, wherein said orthogonal ion accelerator includes one without grids (grid-less).

47. The mass spectrometer as defined in claim 45, wherein the second MR-TOF MS forming said TOF MS comprises a plurality of deflectors cooperating with a lenses in said drift space to adjust a flight path of the ions in said TOF MS.

48. A tandem multi reflecting time-of-flight mass spectrometer (MR-TOF MS-MS) comprising a first MR-TOF MS for separating parent ions, a fragmentation cell attached to said first MR-TOF MS for receiving said parent ions, and a second MR-TOF MS attached to said fragmentation cell for mass analysis of daughter ions exiting said fragmentation cell, wherein at least one of said MR-TOF MS comprises at least two grid-less and parallel ion mirrors separated by drift space and substantially elongated in one-shift-direction.

49. The tandem MR-TOF MS as defined in claim 48, wherein at least one of said first and second MR-TOF MS comprises the features defined in claims 1-32.

50. The tandem MR-TOF MS as defined in claim 48, further comprising a timed ion selector between said first MR-TOF MS and said fragmentation cell.

51. The tandem MR-TOF MS as defined in claim 48, wherein said fragmentation cell further comprises at least one set of electrodes connected to one of DC and slow varying voltage to form one of a respective axial DC electric field or an axial moving-wave electric field, controlling velocity of ion motion within said fragmentation cell, and said DC voltage being applied to at least one electrode in said at least one set as RF voltage.

52. The tandem MR-TOF MS as defined in claim 48, wherein said fragmentation cell further includes a gas at a gas pressure (P) above P*L> 0.2 Torr*cm.

53. The tandem MR-TOF MS as defined in claim 48, wherein said fragmentation cell comprises a differential pumping stage and an ion focusing assembly.

54. The tandem MR-TOF MS as defined in claim 48, wherein said fragmentation cell comprises at least one gas-filled set of electrodes having a radio frequency (RF) voltage applied to at least one electrode within said set of electrodes to confine ions in a radial direction.

55. The tandem MR-TOF MS as defined in claim 48, wherein said fragmentation cell comprises means for ion storage and pulsed ejection, in one of an axial and an orthogonal direction.

56. The tandem MR-TOF MS as defined in claim 52, wherein said second TOF MS comprises an orthogonal ion accelerator.

57. The tandem MR-TOF MS as defined claim 55, wherein said second MR-TOF MS comprises means for adjusting an ion path less than, and an acceleration voltage greater than, said first MR-TOF MS such that a flight time in said TOF MS is at least 100-fold less compared to said flight time in said first MR-TOF MS.

58. The tandem MR-TOF MS as defined in claim 54, wherein said second MR-TOF MS comprises a data system providing parallel acquisition of daughter spectra without mixing spectra from unrelated parent ions.

59. The tandem MR-TOF MS as defined in claim 58, wherein said second MR-TOF MS comprises a lense assembly disposed within said drift space.

60. The tandem MR-TOF MS as defined in claim 59, wherein said lenses assembly comprises at least one deflector configured to adjust a flight path of ions in said second MR-TOF MS.

61. A tandem multi-reflecting time-of-flight mass spectrometer (MR TOF MS-MS) comprising: a MR-TOF MS, and a fragmentation cell connected said MR-TOF MS and configured to revert ions within said MR-TOF MS to employ the same MR-TOF analyzer for analysis of both parent ions and fragment ions, wherein said MR-TOF MS comprises an assembly of two grid-less and parallel ion mirrors separated by drift space and substantially elongated in one-shift-direction.

62. The tandem multi-reflecting time-of-flight mass spectrometer as defined in claim 61 comprising one or more of the structures defined in claims 1 through 32.